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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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David M. Goldenberg

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EXAMINER

BRISTOL, LYNN ANNE

ART UNIT

PAPER NUMBER

1643

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DELIVERY MODE

08/13/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/680,734	Applicant(s) GOLDENBERG ET AL.	
	Examiner LYNN BRISTOL	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44, 50, 113 and 116-122 is/are pending in the application.
- 4a) Of the above claim(s) 44 and 50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 113 and 116-122 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/5/09 has been entered.
2. Claims 44, 50, 113 and 116-122 are all the pending claims for this application.
3. Claims 51, 111, 114, and 115 were cancelled and new Claims 116-122 were added in the Response of 6/5/09.
4. Claims 44 and 50 are withdrawn from examination.
5. Claims 113 and 116-122 are all the claims under examination.
6. Applicants amendments to the claims have necessitated new grounds for objection and rejection.

.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement (1)

7. The rejection of Claims 111 and 114 (and new Claim 15) under 35 U.S.C. 112, first paragraph, in lacking enablement for any combination therapy producing a

Art Unit: 1643

synergistic effect in treating human medullary thyroid carcinoma or human colorectal cancer is moot for the cancelled claims.

Enablement (2)

8. The rejection of Claim 114 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for using any IgG1 anti-Class III CEA antibody to sensitize a human medullary thyroid carcinoma or human colorectal cancer in vivo to DTIC or CPT-11 much less where the subject is a human is moot for the cancelled claim.

New Grounds for Objection

Claim Objections

9. Claims 116, 121 and 122 are objected to because of the following informalities:

a) Claim 116 is objected to in the recitation of “the corresponding framework region sequences (FRs)” and in order to substantially improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.*, “the corresponding framework region (FRs) residues”.

b) Claim 121 is objected to for duplicate recitation for the species “a stem cell growth factor.”

c) Claim 122 recites a Markush group for what appear to be two groups of radionuclides. For example, “³²P... ²¹²Pb”, and “²¹³Bi... and ²⁵⁵Fm.” It is unclear if the ordinary artisan should select one radionuclide from the first group and another from the

Art Unit: 1643

second group, or whether the insertion of "and" between both groups is a typographical error. Clarification is requested.

Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 120 and 121 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 120 recites the limitation "the toxin". There is insufficient antecedent basis for this limitation in the claim.

b) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required

Art Unit: 1643

feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 121 recites the broad recitation “a stem cell growth factor”, and the claim also recites “S1 factor” which is the narrower statement of the range/limitation. Another example includes “an interferon (IFN)” followed by “interferon-a, interferon-B, interferon-γ.” It is suggested that the subspecie(s) for the specie(s) of immunomodulator are cancelled in Claim 121.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

11. Claims 113 and 116-122 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the humanized MN-14 antibody having the CDRs and FRs for the clone used in the Examples and shown as having the ability to sensitize the CEA-expressing cancers, human medullary thyroid carcinoma or human colorectal cancer, to DTIC or CPT-11, does not reasonably provide enablement for any hMN-14 antibody having at least one amino acid substituted from the corresponding framework of the murine HM-14 antibody with any one or any combination of heavy chain amino acid residues 24, 28, 30, 48, 49, 74 and/or 94. The specification does not enable any person skilled in the art to which it pertains, or with

Art Unit: 1643

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 113 and 116-122 are interpreted as being drawn to a composition comprising the hMN-14 antibody comprising the CDRs from the murine MN-14 antibody (Claim 113), and further wherein the hMN-14 antibody has at least one amino acid substituted from the corresponding framework of the murine HM-14 antibody with any one or any combination of heavy chain amino acid residues 24, 28, 30, 48, 49, 74 and/or 94 (Claim 116) (MPEP 806.04(d) "In general, a generic claim should require no material element additional to those required by the species claims, and each of the species claims must require all the limitations of the generic claim." In other words, a generic claim embraces all species claims). Additionally, the amino acid substituted-framework modified hMN-14 antibodies must also possess the function of sensitizing the CEA-expressing cancers, human medullary thyroid carcinoma or human colorectal cancer, to DTIC or CPT-11.

Art Unit: 1643

The relative skill in the art is a molecular immunologist.

Disclosure in the Specification

At [0098], the specification make the general disclosure:

"...the MN-14 monoclonal antibody or fragment thereof is a humanized or fully human MN-14 antibody or fragment thereof. The framework regions (FRs) of the light and heavy chain variable regions of the humanized MN-14 antibody or fragment thereof preferably comprise at least one amino acid substituted from the corresponding FRs of a murine MN-14 monoclonal antibody. Still preferred, the humanized MN-14 antibody or fragment thereof comprises at least one amino acid from the corresponding FR of the murine MN-14 antibody selected from the group consisting of amino acid residue 24, 28, 30, 48, 49, 74 and 94 of the murine heavy chain variable region (KLHuVhAIGA) of FIG. 14A-C as noted above. The amino acid sequence of a preferred humanized heavy chain variable region is also set forth in Hansen et al., U.S. Pat. No. 5,874,540, which is incorporated by reference in its entirety. Also preferred, the humanized heavy chain variable region comprises the amino acid sequence set forth in FIGS. 14A-C, designated as KLHuVhAIG and KLHuVhAIGAY. In another embodiment, the humanized MN-14 antibody or fragment thereof comprises at least one amino acid from the corresponding FR of the murine MN-14 light chain variable region. Most preferably, the humanized MN-14 antibody or fragment thereof comprises the light chain variable region of FIG. 13A or FIG. 22A or FIG. 23A.

The working examples in the specification show a DTIC and/or CPT-11-sensitizing effect on the CEA-expressing tumors, human medullary thyroid carcinoma or human colorectal cancer, using a single hMN-14 clone, which is understood by the examiner to represent the sequence shown in Figure 14A-C. Accordingly, the specification does not nearly enable the genus of antibodies meeting all of the structural requirements for the instant claims and that would necessarily result in an antibody meeting all of the functional limitations for the composition claim. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to *make and use* the claimed antibody in a manner reasonably correlated with the scope of the claims broadly including any combination of amino acid substitutions to the framework and having all of the required functionalized properties. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Prior Art Status: interaction(s) between CDR and framework residues that effect binding is unpredictable and requires experimentation

The art recognizes that changes to the framework residues of the variable domains could in fact influence the binding properties for an antibody. Here in the instant case, the claims encompass any combination of amino acid substitutions for corresponding residues from a parent murine MN-14 antibody at residue positions 24, 28, 30, 48, 49, 74 and/or 94, and which is required to a) maintain binding and b) sensitize the CEA-expressing cancers, human medullary thyroid carcinoma or human colorectal cancer, to DTIC or CPT-11. Applicants specification does not teach much less suggest the possibility of antibodies that can meet all of these functional requirements.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

De Pascalis *et al.* (The Journal of Immunology (2002) 169, 3076-3084; cited in the IDS of 9/9/08) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Applicants have not established which of any combination of

Art Unit: 1643

substituted residue positions 24, 28, 30, 48, 49, 74 and/or 94 according to Claim 116 is essential for binding *and* sensitizing.

Casset *et al.* ((2003) BBRC 307, 198-205) constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design, and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* ((2002) J. Mol. Biol. 320, 415-428; cited in the IDS of 9/9/08) state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Wu *et al.* (J. Mol. Biol. (1999) 294, 151-162; cited in the IDS of 9/9/08) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

The references seem to indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there appears to be only the single humanized

Art Unit: 1643

MN-14 clone shown in the working examples that binds antigen and sensitizes as broadly claimed or suggested.

The artisan of ordinary skill in the art would have been required to produce the combination of substitutions in the FR domains by performing the mutagenesis, produce and express the humanized antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody), and then finally perform bioassays in vitro and in vivo to identify any one or more of the instant claimed functional characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate the genus of FR- modified humanized MN-14 antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the framework substitutions encompassed by the claims would result in *just any* humanized antibody clone having retained antigen binding and tumor sensitizing activity for the original antigen (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))).

Conclusion

12. No claims are allowed.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority